Blood biomarkers for occupational hand-arm vibration exposure

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Abstract

INTRODUCTION

Hand-arm vibration is a common occupational exposure that causes neurological impairment, myalgia and vibration induced Raynaud's phenomena or vibration white fingers. The pathological mechanism is largely unknown, though several mechanisms have been proposed, involving both immunological vascular damage and defective neural responses.

AIM

The aim of this study is to test whether the substances IL-33, MDC, IL-10, ET-1, CCL20, calcitonin and TXA_2 change in exposed individuals before and after occupation hand-arm vibration exposure.

Method

Thirty-eight full-time shift workers exposed to hand-arm vibration were recruited. All the participants underwent medical examinations regarding symptoms of Raynaud's phenomena. The concentration of IL-33, MDC, IL-10, ET-1, CCL20, calcitonin and TXA_2 was tested before and after a workday.

Result

There was a significant increase in ET-1 and calcitonin concentration after the work shift. There was also a significant decrease in CCL20 concentration. Moreover, there was significant increase in MDC after the work shift in those exposed to vibration white fingers. Lastly, MDC was statistically significant lower before a work shift (p=0.023) in the vibration white finger group compared to the non-vibration white finger group.

Conclusion

Exposure to occupational hand-arm vibration is associated with changes in ET-1 and calcitonin concentrations and MDC is increased in participates suffering from vibration white fingers, suggesting a role in the pathophysiology.

Background

Hand-arm vibration (HAV) is a common occupational exposure mainly affecting the hands of individuals using vibrating tools [1]. HAV may give rise to Raynaud's phenomenon (RP), neurological impairment and myalgia in the hands [2, 3].

RP is one of the most well-recognized complications from HAV exposure [4, 5]. RP caused by HAV is a secondary form of RP, with known cause and is also referred to as vibration white fingers (VWF) [6].

The normal physiological response to a decrease in the external temperature of the hand is vasoconstriction. RP can be described as an abnormal reaction to cold where vasoconstriction impairs blood flow, causing ischemic white fingers [6, 7]. RP occurs more often in women, as primary RP (without known cause) or secondary RP in rheumatic disease [8-10]. For secondary RP there is a wide range of conditions that can be the underlying cause, such as rheumatic, hematological or endocrine disease, medication, nicotine, vascular injuries, frostbite and HAV [6, 10-14].

The pathological mechanisms of secondary RP caused by HAV, or VWF, are largely unknown, with respect to how HAV affects vessels or nerves, causing an abnormal reaction in blood vessels [2]. Several mechanisms have been proposed, involving a maladaptive neural response, increased blood viscosity, endothelial damage from free radical formation or a direct effect of HAV [5, 9, 15].

Soluble biomarkers of vasoconstriction and immune system activation, systems thought to be implicated in RP, can be measured in plasma. Previous studies have measured such biomarkers in exposed individuals. Vasoconstrictor endothelin 1 (ET-1), platelet-derived thromboxane A_2 (TXA_2), chemokines involved in immune signaling, such as chemokine (C-C motif) ligand 20 (CCL20) and macrophage-derived chemokine (MDC), as well as biomarkers of bone metabolism, such as calcitonin, have been implicated in the pathophysiology of VWF [16-22]. In this study, we aimed to examine whether plasma concentrations of these biomarkers differed in workers using vibrating tools, based on the presence or absence of symptoms of RP.

Aim

The aim of this study is to test whether the substances interleukin 33 (IL-33), MDC, interleukin 10 (IL-10), ET-1, CCL20, calcitonin and TXA_2 change in individuals before and after occupational HAV exposure.

Methods

Thirty-eight (38) full-time shift workers working in a Swedish foundry were recruited. Sixty-eight (68) subjects were invited to participate and 38 accepted (56%). The work tasks that include HAV exposure mainly involved metal grinding. Of the 38 who choose to be included three were excluded from further analysis either because no blood sample was retrieved (n=2) or suspicion of rheumatic disease as cause to the RP.

The participants underwent a medical investigation using a standardized examination according to Ekenvall L, including a medical examination of neck, shoulders and elbows and an examination of vascular and neurological function of the hands [23]. Phalen's, Tinel's and Allen tests were performed to evaluate signs of carpal tunnel syndrome and impaired blood flow to the hands. As a complement to the medical examination, a questionnaire on symptoms related to hand-arm vibrations was answered by all participants. This questionnaire is available in Swedish from the occupational medicine method collection (http://fhvmetodik.se/wp-content/uploads/2014/10/frageformular_hand_arm.pdf).

Whole blood was collected by venepuncture on the right arm, in a vacutainer tube containing an ethylenediaminetetraacetic acid (EDTA) additive, before and after the work shift. Samples were mixed on a rocker for 30 seconds and then centrifuged at 10°C at 1500×*g* for 15 minutes. Resulting supernatant was transferred to an Eppendorf tube and subsequently kept on dry ice at approximately -70°C. At the end of the workday, samples were stored in a -80°C freezer, before being sent to the laboratory in containers containing dry ice. Upon arrival to the laboratory the samples were immediately transferred to a -80°C freezer where they were kept until analysis.

Quantification of macrophage-derived chemokine (MDC or CCL22), CCL20, ET-1 and IL-10 were performed using ELISA kits from R&D Systems (DMD00, DM3A00, DET100 and D1000B, respectively, Minneapolis, MN, USA). Quantification of TXA_2, IL-33 and calcitonin were performed using ELISA kits from Biomatik (EKU07649, Kitchener, Ontario, Canada), abcam (ab108918, Cambridge, UK), Thermo Scientific (EHIL33, Waltham, MA, USA) and Cusabio (CSB-E05131h, Houston, TX, USA), respectively. All ELISAs were performed according to manufacturer's instructions. The optical densities (O.D.) were read at 450 nm with a wavelength correction at 540 nm in a Multiscan Ascent V1.24 with Ascent Software Version 2.6 (Thermo Scientific, Waltham, MA, USA). Data values were expressed as pg/mL deduced from the standard curve after subtracting the blanks, using a 4-parameter logistic algorithm.

To assess the vibration exposure before and after the blood sample was collected, an occupational hygienist performed field measurements at the worksite. The main source of vibration exposure was from grinding machines and exposure was estimated by measuring the vibration level at a point on the handle (or close to where the operator placed his hand) according to ISO 5349-1:2001 [24]. A triaxial accelerometer (3023M2 Dylan Instruments, LA) was fastened on a mounting block and the block was attached to the grinder with hose clamps. The handheld four-channel vibration analyzer (Svantek 106, Svantek, Warzaw, Poland) was used to collect data from the accelerometer.

The study protocol was approved by the Regional Ethical Review Board in Uppsala, Sweden (Dnr 2016/044).

Descriptive statistics were used to assess baseline characteristics of the population.

To test blood samples before and after the workday the Wilcoxon signed-rank test was used to test statistical significance due to the non-normal distribution of the material. A p-value less than 0.05 was considered significant. Statistical software SPSS 25.0 (IBM, North Castle, NY) was used for hypothesis testing.

Results

All the participants were male with a mean and median age close to 45 years (mean 44.6, median 45). Employment time was between 1–37 years with a mean and median of 13.2 and 13.5 years respectively (table 1). The group with VWF had lower mean and median employment time compared to the non-VWF

group. Only five participants were smokers but 14 were using snus (non-smoking Swedish tobacco). The tobacco use was lower in the VWF group.

Table 1. Descriptive data of the study group.

		VWF		non-VWF		Total	
		N	%	N	%	N	%
Sex	Men	22	100	16	100	38	100
Age	<=40	7	31.8	5	31.3	12	31.6
	41–50	9	40.9	5	31.3	14	36.8
	51+	6	27.3	6	37.5	12	31.6
	Mean	*44.8*		*45.1*		*44.6*	
	Median	*45.5*		*46.0*		*45*	
	Min–Max	*26–58*		*28–62*		*26–62*	
Employment year	0–5	4	18.2	2	12.5	6	15.8
	6–10	6	27.3	3	18.8	9	23.7
	11–15	2	9.1	6	37.5	8	21.1
	>15	10	45.5	9	31.3	15	39.5
	Mean	*12.7*		*13.9*		*13.2*	
	Median	*12.0*		*14.0*		*13.5*	
	Min–Max	*1–33*		*1–37*		*1–37*	
Smoking	Never smoking	19	86.5	12	75	31	81.6
	Smoking	2	9.0	3	18.8	5	13.2
	Don’t know	1	4.5	1	6.2	2	5.3
Non-smoking tobacco*	Never used	15	68.2	8	50.0	23	60.5
	User	7	31.8	7	44.0	14	36.8
	Unknown			1	6.0	1	2.6

*Swedish snus

The group with VWF had worked at the worksite longer but total year of vibration exposure was calculated to 19.0 years of exposure for white finger compared to 19.8 years of exposure for non-white fingers. The vibration exposure during the workday when the blood sample were taken was 1.7 m/s^2 for white fingers and 1.3 m/s^2 for non-white fingers (table 2).

Table 2. Exposure data regarding hand-arm vibration for the study participants.

	White fingers	N	Mean	Median	Min	Max	Std. Deviation
Year of vibration exposure at this work	no	16	5.9	0.5	0	34	10.46
	yes	22	6.3	2	0	25	7.99
	total	38	6.1	1.5	0	34	8.98
Total year of vibration exposure	no	16	19.8	14.5	5	38	11.21
	yes	22	19.0	17	5	33	9.15
	total	38	19.3	16	5	38	9.93
Acute vibrations exposure (m/s^2)*	no	16	1.3	1.3	0	3.1	0.87
	yes	22	1.7	1.8	0	3	0.89
	total	38	1.6	1.5	0	3.1	0.89

*Depending on work task during the day, the vibration exposure ranged between 0.1–3.1 m/s^2

For all 35 participants there was a significant increase in ET-1 and calcitonin concentration after work shift. There was also a significant decrease in the CCL20 concentration. For TXA_2 there was a non-significant decrease and a non-significant increase for MDC and IL-10 (table 3).

In the non-VWF group there was a significant decrease in CCL20 and non-significant decreases in TXA_2 and MDC. ET-1 and calcitonin were increased, though this was non-significant.

There was a significant increase in MDC after the work shift for the VWF group and non-significant increase for IL-10, ET-1 and TXA_2. In addition, there was a non-significant decrease for CCL20. MDC concentration differed according to group, showing an increase in the VWF group and a decrease in the non-VWF group.

MDC was statistically significant lower before a work shift (p=0.023) in the VWF group compared to the non-VWF group. TXA_2 was non-significantly increased in the white fingers group before a work shift (p=0.074) and significantly increased after a shift compared to non-white fingers.

Table 3. Change in concentration of the tested biomarkers during the shift. The Wilcoxon signed-ranks test is used to calculate the p-value.

		Mean	Median	Min	Max	Std. Deviation	p-value
Total N=35							
IL 33 (pg/mL)	before	157.5	12.9	0.001	682.1	233.5	
	after	158.8	11.7	0.001	646.4	229.5	0.54
MDC (pg/mL)	before	541.8	526.7	278.0	803.1	128.8	
	after	557.0	566.1	278.6	782.9	117.5	0.09
IL 10 (pg/mL)	before	1.5	1.0	0.001	6.1	1.7	
	after	2.9	1.1	0.001	25.1	4.7	0.12
Endotelin-1 (pg/mL)	before	1.1	0.9	0.6	2.8	0.5	
	after	1.3	1.0	0.6	3.7	0.6	0.02
CCL20 (pg/mL)	before	17.7	12.3	4.7	75.0	15.6	
	after	11.4	10.2	3.6	28.3	5.9	0.02
Calcitonin (pg/mL)	before	11.0	10.1	0.001	38.8	9.3	
	after	14.1	13.9	0.001	32.8	8.8	0.02
Tromboxan A2 (pg/mL)	before	632.6	328.8	52.7	4019.9	794.8	
	after	588.4	355.6	43.3	4019.9	746.1	0.91
Non-VWF N=15							
IL 33 (pg/mL)	before	171.0	15.3	1.2	549.0	218.2	
	after	155.8	14.2	1.9	555.1	208.1	1.00
MDC (pg/mL)	before	596.4	632.9	385.2	803.1	121.6	
	after	569.1	577.1	278.6	782.9	145.8	0.36
IL 10 (pg/mL)	before	1.9	1.3	0.001	6.1	2.1	
	after	3.8	1.1	0.001	25.1	6.6	0.38
Endotelin-1 (pg/mL)	before	1.1	0.9	0.6	2.8	0.6	
	after	1.3	1.2	0.8	2.6	0.5	0.24
CCL20 (pg/mL)	before	16.5	14.5	4.7	55.6	12.6	
	after	10.4	10.4	5.2	15.9	3.3	0.02
Calcitonin (pg/mL)	before	11.9	8.8	0.001	34.8	10.3	

	after	15.7	18.2	1.7	32.8	8.9	0.19
Tromboxan A2 (pg/mL)	before	459.3	125.9	52.7	1811.9	587.5	
	after	332.9	165.5	44.0	920.3	304.0	0.43
VWF N=20							
IL 33 (pg/mL)	before	147.4	7.8	0.001	682.1	249.5	
	after	161.2	11.1	0.001	646.4	249.7	0.38
MDC (pg/mL)	before	500.8	493.4	278.0	799.2	121.1	
	after	547.9	549.5	364.1	725.8	94.1	0.006
IL 10 (pg/mL)	before	1.3	0.9	0.001	4.8	1.4	
	after	2.1	1.5	0.001	7.6	2.4	0.20
Endotelin-1 (pg/mL)	before	1.0	0.9	0.7	2.1	0.4	
	after	1.2	1.0	0.6	3.7	0.7	0.06
CCL20 (pg/mL)	before	18.6	11.3	5.9	75.0	17.8	
	after	12.1	9.3	3.6	28.3	7.2	0.26
Calcitonin (pg/mL)	before	10.4	11.1	0.001	38.8	8.7	
	after	12.9	11.7	0.001	31.8	8.9	0.08
Tromboxan A2 (pg/mL)	before	762.7	488.1	57.7	4019.9	913.5	
	after	780.0	400.0	43.3	4019.9	915.3	0.42

Discussion

In this study we analyzed plasma concentrations in blood sample of workers that are affected by HAV exposure, and that are believed to be implicated in the pathophysiology of VWF. For several of the analytes we found changes in the concentration before and after the shift when comparing the VWF and non-VWF groups. ET-1, showing a significant increase for the whole study population, is a known vasoconstrictor, and thus reflects an increased vasoconstriction, possibly due to the exposure from HAV. The baseline concentration of ET-1 did not differ between the VWF and non-VWF groups before the work shift. These findings differ from earlier studies that have shown different results in the baseline, with lower ET-1 concentration in VWF (VWF or other HAV-exposed complications) compared with controls [25, 26]. It was theorized that a lower baseline ET-1 can be a compensatory mechanism as an response to vibration damage [16]. Exposure to cold has similarly been reported to cause an increase in ET-1 [16, 25]. We found a significant increase for the whole exposed population, which concords with the notion that

HAV exposure has a vasoconstrictive effect. Of note is that the daily exposure in this study is relatively low, below the action value of 2.5 m/s^2, which is often used as a legislate value in both the European Union and the UK.

CCL20 was significantly decreased in the non-VWF group but was non-significantly lowered in VWF, when comparing concentrations before and after the shift (Table 3). CCL20 is an inflammatory chemokine that is implicated in several inflammatory conditions [18]. In vitro experiments have found that CCL20 interacts with myostatin. Myostatin enhances the secretion of CCL20, and lower levels might reflect an inhibition of myostatin via the myostatin-CCL20-CCR6 axis [27]. Myostatin is involved in inflammatory joint diseases and degenerative muscle diseases, and a decrease in Mycostatin concentration has the potential to induce an anti-inflammatory response and muscle hypertrophy [27, 28]. The decrease of CCL20 might reflect an effect of vibration on tissues, inhibiting the inflammatory response to promote muscle tissue repair. This would explain why the results were significant for the whole group but not significant in the VWF group where symptoms of disease are present.

IL-33 and IL-10 showed no changes after exposure, which suggests that these cytokines are not affected by HAV exposure. IL-33 is a signal of cell damage. The lack of change in concentration is consistent with the idea that HAV exposure does not mainly cause cell damage, and that the main pathophysiological mechanism is related to vasoconstriction [19]. IL-10 increased non-significantly, and other studies have found a higher serum level to correlate with RP symptoms in systemic sclerosis patients with newly debuted RP, suggesting its involvement in the early stages of RP [29].

There was a significant increase in calcitonin after the work shift and a non-significant increase in both the VWF and the non-VWF groups. Calcitonin decreases serum Ca^{2+} by bone resorption via osteoclasts and enhances Ca^{2+} excretion by the kidneys [30]. HAV exposure is suspected to induce bone cyst via micro fractures, especially from single impacts (when working with impact tools), even if the results are conflicting [31]. An increase in calcitonin could be a response to an increased blood Ca^{2+} from micro fractures from the HAV exposure [32, 33].

As for MDC, there was a significant increase in the VWF group after exposure and a non-significant decrease in the non-VWF group. There was also a lower concentration in the VWF group compared to the non-VWF group. MDC is produced by monocyte-derived dendritic cells and has chemotactic effects to attract immune cells [34]. Macrophages and other innate immune system cells have been suggested to play a pathogenic role in early scleroderma – a disease that has similar symptoms to VWF [34]. Our results could be explained by MDC attracting innate immune cells that have pathogenic effects [35]. Reports of serum levels of MDC being increased in systemic sclerosis, but not in systemic lupus erythematosus (SLE) – both diseases that includes symptom of RP – could be indicative of differing mechanisms in the pathogenesis of RP, depending on disease [36]. This suggests that systemic sclerosis and VWF share pathophysiologic features that differ from those of SLE.

A non-significant increase in TXA_2 was observed for all study groups. However, both before and after exposure, higher concentrations were observed in the VWF group compared to the non-VWF group. This contradicts earlier studies showing no different in TXA_2 concentration between VWF and controls [25, 37]. In primary RP patients, increased TXA_2 production from platelets induce vasoconstriction [38]. Our results could suggest that participants with VWF can have a tendency for primary RP or more active platelets that produce TXA_2. In other studies, TXA_2 has been found elevated and increased with the severity of the RP that is secondary to rheumatic disease [17, 39]. The increase in TXA_2 in our result might be due to those exposed to HAV acquired an ischemic environment due to vasospasm in the fingers which, via ROS production, increases TXA_2 – which could then explain why there is no increase in concentration during the shift for the VWF group where there already are an ischemic environment [40].

A strength with this study is that all participants were medically examined by the same physician and under the same circumstances. Samples were collected before and after shifts regardless of the time of day (morning and afternoon shift). The HAV exposure was measured in all participants during the day, between the collections of the blood samples. The limitation of this study is the rather small study population which was stratified into two groups. We also do not have data on HAV exposure during the days prior or non-work-related exposure in the study, which could affect the baseline values of the biomarkers. The daily exposure from HAV in our population was below the legislative limit set by government regulation, of 2.5 m/s2, and the low levels of exposure could be too low to detect changes in physiology or plasma biomarker concentrations. On the other hand, our results call the accepted limit of exposure into question, as levels of exposure below the cut-off (median exposure of 1.8 m/s2) had measurable, statistically significant effects on the exposed. We also did not control for confounding factors such as ergonomics, airborne particles, noise or skin contamination from industrial exposure. Our results warrant further studies in which health outcomes in individuals subjected to exposures below the legislative limit are studied, in order to assess the risk associated with lower exposures and whether the limit should be adjusted.

Conclusion

HAV exposure is associated with significant changes in ET-1 and calcitonin concentration, which suggests that vasoconstriction and Ca2 + metabolism are involved in the response to HAV, even in low doses. In the VWF group, an increase in MCD compared to the non-VWF group suggests that MCD is involved in VWF pathophysiology. Despite exposures below the legislative action value, physiological and biomarker changes were observed, which calls the suitability of the current limit level into question.

Declarations

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Declaration of interest

The authors declare that they have no interest of conflict, commercial or non-commercial.

Availability of data and material

The data used in this study was derived from Patients data Access to data. Any researcher, granted that they have an ethical approval from a regional ethical board, can contact Department of Environmental and Occupational Medicine at Örebro University Hospital (USÖ) for the studydata. However, the Swedish National Board of Health and Welfare will also put restrictions on sharing sensitive information.

Authors' contributions

PV and PG conceived and designed the study. PV did the medical examination and data collection. IB did the main data analysis and PV,OL,PP,NJ and PG interpreted the results. All authors participated in the writing of the manuscript and approved the final version.

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Ethics approval, Consent to participate

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the Regional Ethical Review Board situated at Uppsala (Dnr 2016/044).

Consent for publication

The final manuscript has been approved by all authors.

Competing Interests

The authors declare that they have no competing interests

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